Predictive Factors of Surgical Site Infection in Prosthetic Joint Surgery. A Prospective Study on 760 Arthroplasties.

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Abstract

Purpose: Surgical site infection (SSI) is a debilitating complication of total joint arthroplasty (TJA) with significant morbidity and increased costs.

Aim of our study was to identify potential risk factors for SSIs in a population of patients undergoing TJA.

Methods: TJA were prospectively recruited at Santa Maria Maddalena Hospital from February 2019 to April 2020. Age, sex, major comorbidities, American Society of Anesthesiologists (ASA) class, length of surgery, type of surgical suture, total hospital length of stay and clinical laboratory data were collected. The study population was then divided into two groups: Group A, normal post-operative course, and Group B, patients who developed SSI at follow-up (17-25 days).

Results: 25/760 (3.3%) patients developed SSIs at follow-up. Clinical and demographic parameters were not different between the two groups. Total leucocyte and neutrophil values at discharge resulted to be significantly higher in Group B compared to Group A ($p=0.025$ and $p=0.016$, respectively). Values of 7860/mL for total leucocyte, and 5185/mL for neutrophil count at discharge significantly predicted the future development of SSI (AUC 0.623 and AUC 0.641, respectively; $p<0.05$) independently from confounding factors (total leukocytes: O.R.=3,69 [95% C.I. 1,63-8,32]; neutrophils: O.R.=3,98 [95% C.I. 1,76-8,97]. Deep SSIs has been diagnosed significantly before superficial SSIs ($p=0,008$), with a median advance of 9 days.

Conclusion: Total leukocytes and neutrophils at discharge seem useful to identify a population at risk for the development of SSIs following TJA. Further studies on larger populations are needed to develop a predictive SSIs risk score that should include those variables.

Background

The number of total joint arthroplasty (TJA) procedures has steadily increased over the past decades, mainly due to demographic changes, with more aged people less willing to accept activity limitations (1). This increased demand of operative procedures implies an increasing number of patients at postsurgical complications risk.

Surgical site infection (SSI) is the second most frequent complication after instability and prosthetic loosening (2, 3) and represents one of the most common healthcare-associated infections (HAI) among orthopedic patients (4). According to some reports, the rate of SSI secondary to TJA is expected to increase by 2–6.5% for hip and 6.8% for knee arthroplasty respectively in the next decades (5), with a consequent increase in the total costs related to treatment (6).

Based on CDC classification (7), organ spaced SSIs, identified as periprosthetic joint infection (PJI), occurs in 1–2% of primary and in 4% of revision arthroplasties (8). It represents an extremely serious

complication, due to the increased patient mortality and morbidity, and a burden that increases the hospital costs (9), estimated to be about twenty-four times higher than the cost of a primary implant (10).

Patients affected by PJI after joint replacement procedures require prolonged antibiotic therapy, revision, or removal of the prosthesis (11), and are at higher risk of impaired functional ability.

Around two thirds of PJI cases are caused through intra-operative inoculation of micro-organisms (12) and the difficulty in their treatment depends on the ability of micro-organisms to grow and persist on the implant surface and on necrotic tissue in the form of a biofilm (13).

Biofilm micro-organisms are up to 1000 times more resistant to growth-dependent antimicrobial agents than their planktonic counterparts. In vitro susceptibility testing with the determination of minimal inhibitory concentrations (MIC) do not reflect the in vivo situation, and in the clinical setup the effective local concentration of many antibiotics cannot be reached by systemic application only (14).

Based on microbial virulence, PJI can be divided into “early” (within the first four weeks after implantation) or “delayed” (typically between three months and three years). Early infections are sustained by high-virulent organisms (e.g. *Staphylococcus aureus*, streptococci, enterococci) and clinically occur local and systemic signs of inflammation. On the contrary, delayed infections are caused by low-virulent pathogens (e.g. coagulase-negative staphylococci or *Cutibacterium* species) and manifest with insidious clinical symptoms such as arthralgia or early implant failure (15).

A conservative treatment performed with DAIR (Debridment, Antibiotic, Implant retention) is only allowed if the infection is diagnosed and treated within one month of implantation of the prosthesis, or within three weeks of the onset of symptoms. To predict outcome of PJI treated with DAIR, the KLIC-score (KLIC-score: Kidney, Liver, Index surgery, Cemented prosthesis and C-reactive protein value) has been formulated as a risk stratification tool (16).

In the updated edition of the CDC guidelines on SSIs prevention (17), a whole chapter is dedicated to the prevention of PJI, remarking how this surgery play an important role especially regarding the burden of possible complications.

Nevertheless, none of the suggested interventions reached conclusive results, highlighting the lack of knowledge on SSIs prevention in arthroplasty.

The aim of our study was to identify potential risk factors for the development of SSIs in a population of patients undergoing TJA which could be used in future SSI prediction scores to guide the clinical follow-up of total joint replacements.

Matherial And Methods

Patients undergoing TJA surgery (hip, knee, shoulder) were prospectively recruited at Santa Maria Maddalena Hospital (Rovigo, Italy) from February 2019 to April 2020.

Patient demographics (age and sex), major comorbidities and medications, American Society of Anesthesiologists (ASA) class (18), length of surgery, type of surgical incision, type of surgical suture, wound dressing and total length of hospital stay were collected from clinical and surgical records. Laboratory tests such as white blood cells count, neutrophils count, hematocrit, hemoglobin, CRP, ESR, total protein and albumin values had been recorded one week before the surgical procedure and at hospital discharge.

SSIs were diagnosed according to the CDC diagnostic criteria (7) and classified in superficial, deep or PJI. Each enrolled patient was evaluated by an infectious disease specialist between the 17th and 25th day after surgery for SSIs surveillance.

The study population was then divided into two groups according to the diagnosis of SSI: Group A, patients with a normal post-operative course, and Group B, patients who developed SSI at follow-up.

For each case of SSI, the clinical symptoms, etiology and antibiotic resistance pattern (when available), type of revision surgery (if performed), and type of antibiotic therapy administered were collected. For patients with PJI treated with DAIR the risk of failure was calculated by the KLIC-score. Data regarding outcome and one year follow-up were also reported.

The research was carried out in accordance with the ethical principles of the Declaration of Helsinki. The Local Ethics Committee "CESC VR-RO" approved the design of this study and all participants gave their written informed consent.

Statistical Analysis

Normality of distribution of continuous variables was assessed by Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean $\pm$ standard deviation and compared by t-test. Not normally distributed variables were expressed as median (interquartile range) and compared with Mann-Whitney U test. Frequencies were reported as percentage and compared by Chi-square test or Fisher's exact test in the presence of a 2x2 contingency table. A mixed ANOVA was used to observe whether the values measured at pre- and post-operative occasions were different between the two groups of patients. The diagnostic accuracy for total leukocytes and neutrophil's count in detecting SSI was determined by a ROC (Receiver Operator Characteristic) analysis. The Youden's J Index (specificity+sensitivity-1), which maximizes the specific and sensitivity, was used to find the cut-off values. The cut-off values were used to calculate the positive predictive value (PPV), the negative predictive value (NPV) and accuracy. A multivariate logistic regression was used to determine the association between high total leukocytes (>7860 cells/ μ L) or high total neutrophil's count (>5185 cells/ μ L) at discharge and the presence of SSI; sex, age and BMI were included in the analysis as possible confounding factors. The analyses were performed by SPSS (IBM) for Windows, version 25. A p-value < 0.05 was considered significant.

Results

Description of the population

During the study period, a total number of 760 TJA were recorded: 432 were total knee arthroplasty (TKA, 56.8%), 325 were total hip arthroplasty (THA, 42.8%) and 3 were total shoulder arthroplasty (TSA, 0.4%). The analyzed surgeries were almost primary arthroplasties (n=730, 96%) in contrast to revisions (n= 30, 4%). A total of 25 out of 760 (3.3%) SSIs were detected: 15 (60%) affected TKA and 10 (40%) THA. No SSI were recorded following TSA and prosthetic revision surgery.

According to CDC's SSIs classification (7), 15 (60%) SSIs were classified as superficial, 6 (24%) as deep and 4 (16%) as PJI.

Clinical and demographic characteristics of Group A and B are summarized in Table 1.

Table 1
Demographics and clinical variables for controls and cases.

	Group A (n=735)	Group B (n=25)
Sex (female; n, %)	478 (65)	18 (72)
Age (years±SD)	71.2±9.5	68.5±13.7
BMI (Kg/m²)	28.6±5.1	30.4±6.7
Diabetes (%)	13.3	9.0
Number of operators		
2	29.0	24.0
3	56.0	56.0
4	14.7	20.0
5	0.1	0.0
Prosthesis Type (%)		
Hip	42.8	40.0
Knee	56.7	60.0
shoulder	0.5	0.0
Cemented (yes, %)	57.8	60.0
Antibiotic (%)		
Cefazoline	94.0	92.0
Vancomicine	6.0	8.0
ASA Score (mean±SD)	2.6±0.5	2.6±0.5
Duration of surgery (minutes; mean±SD)	74±19	76±17
Steroid drugs (%)	4.4	4.0
Anticoagulant therapy (%)	31.2	31.8
Hospitalization (days, mean±SD)	13.0±2.9	13.0±2.8
Type of suture (%)		
Clip	14.7	20.0
Absorbable stitches	85.3	80.0
SD: standard deviation		

No statistically significant differences were observed between the two groups for any of the investigated parameters. Patients in both groups were more likely to be female (Group A 65% vs. Group B 72%, $p=0.47$) and severely overweight (mean BMI; Group A 28,6 vs. Group B 30,4, $p=0.101$). Most procedures were performed by 3 orthopaedic surgeons. Mean duration of surgeries was 74 minutes for group A and 76 minutes for Group B. Mean duration of hospitalization was 13 days for both groups.

A cefazoline-based antibiotic prophylaxis was used in most cases. Patients who were allergic to cefazoline or with known risk factors for MRSA colonization received vancomycin-based antibiotic prophylaxis.

Laboratory test parameters differ in those patients contracting SSI

Results from laboratory tests performed in both pre-operative period and at discharge are reported in Table 2. Total leucocyte and neutrophil values at discharge were significantly higher in Group B compared to Group A ($p=0.025$ and $p=0.016$, respectively). Despite not reaching statistical significance ($p=0.087$), the difference in CRP values between the two groups suggests that this test may play a role in defining patient with a higher risk of developing SSI as well.

Table 2
Laboratory parameters measured before the surgical procedure and at discharge.

	Control (n=735)		Infected (n=25)	
	Pre-operative	Discharge	Pre-Operative	Discharge
Pre-operative serum Albumin	4.6 [4.4-4.8]	-	4.5 [4.2-4.7]	-
Pre-operative CRP	17.0 [7.0-37.0]	86.0 [40.0-157.0]	21.0 [5.5-59.5]	123.0 [69.5-176.0]
Pre-operative ESR	16.0 [9.0-28.0]	45.0 [30.0-62.0]	12.0 [6.0-25.0]	43.0 [27.0-63.5]
Total leukocytes (cells/μl)	6690 [5720-8020]	6720 [5770-7870]	7030 [5560-8545]	7970 [6235-9680] ^a
Neutrophils count (cells/μl)	4010 [3200-4930]	3880 [3160-4920]	4320 [3305-5100]	4900 [3650-5885] ^b
Values are reported as median [interquartile range]; SD: standard deviation; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. ^a $p=0.025$ vs. control; ^b $p=0.016$ vs. control				

We tested the diagnostic accuracy of total leukocyte and neutrophil's count at discharge to detect those subjects at risk to develop SSI by ROC curves analysis and area under the curve (AUC) calculation (Figure 1). AUC values were 0.623 ($p=0.025$) and 0.641 ($p=0.016$), respectively. By calculating the Youden's J Index, which maximizes the sensitivity and specificity, we found a cut-off value for total leukocyte of

7860 cells/ μ L (sensitivity/specificity: 56%/75%) and for neutrophil's count of 5185 cells/ μ L (sensitivity/specificity: 48%/80%). The two variables showed a high negative predictive value (NPV; leukocytes: 98.03%; neutrophils: 97.85%); however, they showed a poor positive predictive value (PPV; leukocytes: 6.97%; neutrophils: 7.69%).

Nonetheless, by a multivariate binary logistic regression analysis we demonstrated that patients with values of leukocytes or neutrophils higher than the cut-off had a higher odd of developing SSI, independently from confounding factors like sex, age and BMI. In fact, patients with a value of total leucocyte at discharge higher than the cut-off had a 3.39 higher risk of developing SSI than those with lower values (O.R.=3,69 [95% C.I. 1,63-8,32]). Similarly, patients with neutrophils value at discharge higher than the cut-off showed a 3.98 higher risk of developing SSI than those with lower values (O.R.=3,98 [95% C.I. 1,76-8,97]).

Finally, to further investigate the relation between these two parameters and the increased risk of developing SSI, we performed a mixed ANOVA analysis. By this mean, we were able to detect a SSI-related growth of values from baseline (pre-operative) to discharge. As expected, the values of total leukocytes, ESR and PCR in the whole population are increased at discharge compared to the pre-operative value ($p=0.002$, $p=0.001$ and $p=0.001$, respectively), whereas neutrophils almost reached the statistical significance ($p=0.056$). However, we found a significant interaction between the pre- and post-operative changes of total leukocytes and future development of infection. As displayed in Figure 2A, patients that will develop infection (Figure 2A, squares) had a steeper increase in total leukocytes compared with not infected subjects ($p=0.006$). Such interaction still exists for neutrophil's count, although it is less evident (Figure 2B, $p=0.019$).

Characteristics of SSI classification

The time-to-diagnosis was compared between the three SSI classification categories (superficial, deep and PJI) through an ANOVA analysis. As displayed in Figure 3, deep SSI was diagnosed significantly before superficial ones ($p=0.008$), with a median advance of 9 days. This difference loose statistical significance when comparing deep SSI and PJIs ($p=0.145$).

According to the clinical presentation of SSI following arthroplasty, dehiscence of the surgical wound occurred in 10 patients (40%), 8 patients (32%) developed fever and 8 cases (32%) required a surgical revision. Three out of four cases (75%) of PJI were treated with DAIR; a KLIC score < 4 was registered in all cases with an expected failure rate between 4.5% and 19.4%.

A two-stage revision was carried only in one case (0.25%).

Twelve cases of SSI (48%) needed a new hospital admission and a parenteral antibiotic therapy; a microbiological diagnosis was disclosed only in 9 cases out of 25 (36%), from synovial fluid and tissue samples ($n=8$) and bloodstream ($n=1$), respectively.

In 5 cases (56%) the etiology of the SSI has been attributed to gram-positive organisms, in 3 (33%) cases to gram-negative ones. A polymicrobial infection was detected only in one case (11%). The most frequently isolated bacterium was *S. epidermidis* (40%), methicillin and fluoroquinolones resistant. Isolated pathogens and resistance patterns are shown in Table 3.

Table 3. Isolated pathogens and their resistance pattern

Pathogen	Number of isolates n(%)	Tested antibiotic	Resistance (%)
S. epidermidis	4 (40%)	Methicillin	100%
		Fluoroquinolones	100%
P. mirabilis	2 (20%)	Fluoroquinolones	0%
		Cotrimoxazole	50%
S. aureus	1 (10%)	Methicillin	0%
		Fluoroquinolones	0%
		Cotrimoxazole	0%
S. agalactiae	1 (10%)	Fluoroquinolones	0%
P. aeruginosa	1 (10%)	Fluoroquinolones	0%
E. cloacae	1 (10%)	Fluoroquinolones	0%

All patients completed a full course of antibiotic therapy (2 weeks for superficial/deep SSIs and 10-12 weeks for PJI). None of the patients with a superficial or deep SSIs relapsed during a one-year follow-up. Two out of 4 PJI (50%) relapsed after a conservative DAIR approach (patients relapsed at 40 days and 3 months from the end of the therapy, respectively); relapsed PJI infections were caused by MSSA and *P. mirabilis*.

Discussion

Surgical site infections represent the most frequent and expensive infectious complication in Europe and USA, as they often require a prolonged hospitalization and sometimes a new surgery, significantly impacting on mortality and morbidity (9).

In the present study, we enrolled a relatively large cohort of patients (n=760) undergoing TJA (hip, knee and shoulder) at Santa Maria Maddalena Hospital, a third level regional reference center for orthopedic surgery.

The comparison between our study population and the Italian epidemiological data available (19) shows a lower percentage of deep SSIs and PJI compared to the national infection rates. In fact, in the Italian

case series, 54% of SSI diagnosed in orthopedic surgery are classified as deep or PJI, while in our population only 40% of SSI match this classification.

It is worth noting that none of the revision surgeries carried out at our institution developed a SSI, although literature data points out that the incidence of this complication is significantly higher following a revision compared to a primary implant (20). The reason for this difference, however, could be found in the small number of revisions performed (4%), compared to primary arthroplasties (96%).

Both sex and mean age of the study population are demographically homogeneous with the results reported in the "National surveillance system of SSIs" (19); the mean BMI of the enrolled population is 29.10 kg/m², explaining how obesity plays a key role in joint arthrosis.

In the comparison of the two study groups, none of the clinical variables considered reached statistical significance. According to literature data, some of the considered variables (eg. BMI, diabetes, steroid and anticoagulant therapy, number of surgeons, duration of surgery, staples) have been associated with an increased risk of developing SSI, an association not found in our study.

On the contrary, the analysis of the main laboratory tests brought some significant results: the total leukocytes and neutrophils count at the time of hospital discharge were significantly higher in group B ($p=0,025$; $p=0,016$, respectively). To our knowledge, the role of total leukocytes and neutrophils at discharge has never been highlighted in literature data as an independent risk factor or the development of SSI following joint replacement.

Cut-off values for total leukocytes $>7860/\mu\text{L}$ and neutrophils $> 5185/\mu\text{L}$ may be able to discriminate the two groups. Although the diagnostic value of these tests appears weak to recommend them as diagnostic tests for SSI, their high negative predictive value (total leukocytes: 98.03%, OR: 3.69; neutrophils: 97.85%, OR: 3.98) suggest their potential role during the post-operative screening, aimed at highlighting patients with a higher risk of developing SSI, alone or as a part of a cluster of variables or a predictive score.

The limit of these two tests lies in the very low positive predictive value (total leukocytes: 6.97%; neutrophils: 7.69%), which suggests the need to integrate further diagnostic exams in the selected population to discriminate infected patients from false positive cases. However, given the crucial one-month deadline to perform a successful DAIR, we believe that rapidly excluding patients at lower risk and concentrating the efforts on the others could be a useful (and potentially cost-effective) solution in the clinical pathway of TJA follow-ups.

By comparing the timing of SSI diagnosis to the CDC classification (7), we found an earlier SSI diagnosis for deep infections compared to the superficial ones ($p=0.008$) and PJI ($p = 0.145$), (Figure 3). Even though in the latter case statistical significance is not reached, a relationship between the time of SSI diagnosis and the tissue depth of the infection itself hasn't been described yet in literature reports yet, except for PJI that rise later in time (7).

The outpatient examination performed by an infectious disease specialist for SSI surveillance was carried out between the 17th and 25th day post-surgery. Data from the enrolled population show that all diagnosed superficial SSI and PJI fall within this observation period. Deep SSI, on the other hand, anticipated the screening period, since many cases were diagnosed before the hospital discharge.

According to the clinical presentation, hyperpyrexia was recorded mainly in patients with deep or periprosthetic SSI.

Among SSI with microbiological diagnosis (n=9), 4/9 cases were supported by a Gram negative bacterium. This element suggests that contamination of the surgical site may have occurred at a time other than the surgical act, presumably due to wrong management of the dressing after discharge. Risk factors for the development of SSIs from Gram negative bacteria are diabetes mellitus and the presence of urinary catheter (21); none of the patients who developed SSI caused by Gram negative bacteria were diabetic, whereas data regarding the placement of a urinary catheter were not collected in this study.

All patients treated for SSIs have completed the planned therapeutic course, without any systemic or local complication. To date, no recurrence has occurred in superficial and deep SSI. The only cases of relapse involved periprosthetic infection treated with DAIR (2/4, 50%) caused by MSSA and *P. mirabilis*, respectively.

In literature, DAIR treatment for PJI shows success rates varying between 32 and 100% (22). DAIR represents an attractive surgical modality for treatment of PJI although protocols differ in several retrospective series and randomized controlled or prospective trials on this topic are lacking. It is well known that the increase in the chances of success of this procedure depends on a careful selection of patients associated to radicality of the surgical toilette.

In the present study, the KLIC score used to stratify the risk of relapse in patients undergoing DAIR has shown poor accuracy for outcome prediction even in patients defined at "low risk" (KLIC score <4); according to our opinion, the main limit of the score is represented by the lack of a microbiologic parameter. Relapsed periprosthetic infections, in fact, were sustained by virulent pathogens (MSSA and *P.mirabilis*, respectively).

Main limitation of our study is represented by the poor PPV of total leukocytes and neutrophils value at discharge that may discourage its application as possible clinical tests to discriminate patients at risk to develop future SSI. This may be partially due to the low sample size of the group of patients presenting with SSI, which unbalanced the study. However, we consider it as a good starting point for studies on larger populations to replicate our findings.

Conclusions

Two clinical variables, total leukocytes and neutrophils at discharge, seem useful to identify a population at risk for the development of SSIs. Further studies on larger populations are needed to develop a

predictive SSIs risk score that should include those variables. In addition, our case series, though limited, seems to discourage the use of KLIC score in its present form as a risk stratification tool in DAIR. Further studies are needed to validate a successful prognostic score for DAIR procedure that consider the addition of bacterial-related variables, such as type of isolated strains and antimicrobial resistance profiles, when available.

Abbreviations

SSI: Surgical site infection;

TJA: total joint arthroplasty;

ASA: American Society of Anesthesiologists;

HAI: healthcare-associated infections;

PJI: periprosthetic joint infection;

MIC: minimal inhibitory concentrations;

DAIR. Debridement, Antibiotic, Implant retention.

Declarations

Fundings

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval and consent to participate

The study was approved by the local ethic committee “CESC VR-RO”. Written informed consents were obtained from all participants before their enrolment.

Consent for publication

All the enrolled subjects had signed a written informed consent for publication.

Availability of data and materials

All the data included in the manuscript are available from the authors upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

MM and GDR equally contributed to the design of the study and the writing of the manuscript. MM CC and AT analyzed and interpreted the patient's data. GAZ and AT performed the statistical analysis. CC, EM, GAZ contributed to the revision of the article. DC contributed to the collection of patient's data. All authors read and approved the final version of the manuscript.

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Figures

Figure 1

ROC curve for the two tests: total leucocytes at discharge and neutrophils at discharge.

Figure 2

Variation of total leucocytes (A) and neutrophils (B) in the two groups between the pre-operative and at discharge measurements.

Figure 3

Time to diagnosis of SSI (days from the operation) in relation to SSI classification.